

Review article

# The pharmacokinetics and different regimens of misoprostol in early first-trimester medical abortion

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## Abstract

Misoprostol is a synthetic prostaglandin E<sub>1</sub> analogue that is commonly used for medical abortion. It can be given orally, vaginally and sublingually. A pharmacokinetic study has shown that sublingual misoprostol has the shortest onset of action, the highest peak concentration and the greatest bioavailability among the three routes of administration. Earlier clinical trials have shown that vaginal misoprostol is superior to oral misoprostol when combined with mifepristone for early first-trimester medical abortion. Recent studies on the clinical efficacy of sublingual misoprostol have demonstrated that it is as effective as vaginal misoprostol. Further studies are required to determine the optimal dose and route of administration of misoprostol that can give the highest complete abortion rate, lowest ongoing pregnancy rate and least side effects. © 2006 Elsevier Inc. All rights reserved.

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## 1. Introduction

Misoprostol (15-deoxy-16-hydroxy-16-methyl prostaglandin E<sub>1</sub>) is a synthetic prostaglandin E<sub>1</sub> analogue. It was developed by Searle in 1973 for the treatment and prevention of peptic ulcer due to its inhibition of gastric acid secretion and its various mucosa-protective properties [1]. Its uterotonic and cervical priming action makes it an important drug in gynecological practice. It has several advantages over other prostaglandin analogues. Firstly, it is less expensive than other prostaglandin analogues. Secondly, it is stable at room temperature and, therefore, does not require refrigeration. Thirdly, since it is licensed for the treatment and prevention of peptic ulcer, it is widely and easily available in many developing countries. Although misoprostol is not licensed for use in abortion, it has been extensively used offlabel as an abortifacient in many parts of the world.

## 2. Pharmacology of misoprostol

### 2.1. Structure and chemistry of misoprostol

Naturally occurring prostaglandin E was found to be capable of inhibiting gastric acid secretion in 1967 [2].

However, there are several drawbacks that limit its clinical applications. Firstly, natural prostaglandin E is rapidly metabolized and, therefore, is not orally active. The duration of action is short even if it is given parenterally. Secondly, natural prostaglandin E is associated with numerous side effects because its actions are not specific. Thirdly, its shelf life is short because of its chemical instability. Misoprostol differs structurally from naturally occurring prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. It appears that the methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, while the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improve its activity when taken orally, increase the duration of action and improve the safety profile of the drug compared to other prostaglandins E [3,4].

### 2.2. Pharmacokinetic studies on the different routes of administration of misoprostol

Limited data on the pharmacokinetics of misoprostol have been published. In particular, only single-dose studies have been reported. Earlier studies concentrated only on pharmacokinetic properties after oral administration since this drug was licensed for oral use in the treatment of peptic

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ulcer. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (deesterification) to form misoprostol acid, the principal and active metabolite of the drug. Clinical studies have shown that vaginal administration is more effective than oral administration for medical abortion [5,6]. Zieman et al. [7] performed the first pharmacokinetic study comparing the oral and vaginal routes of administration. Various pharmacokinetic properties (including peak concentration, time to peak concentration and the area under the serum-concentration-vs.-time curve) after vaginal or oral administration of 400 µg of misoprostol were compared. Following a single dose of oral administration, plasma misoprostol levels increased rapidly and peaked at about 30 min. However, the plasma levels declined rapidly by 120 min and remained low thereafter. In contrast, after vaginal administration, plasma concentration gradually increased, reaching maximum levels after 70–80 min and slowly declining with detectable levels present beyond the 6-h study period. The peak concentration achieved following oral administration was higher than that following vaginal administration. The area under the plasma-concentration-versus-time curve (AUC) represents the bioavailability of misoprostol. The AUC after vaginal administration was significantly greater than that following oral administration. The greater bioavailability of vaginal misoprostol may help explain why vaginal administration was more effective for medical abortion. However, it was shown in the same study that the coefficient of variation of the AUC after vaginal administration was greater than that after oral administration. This meant that the absorption of misoprostol through the vaginal route was less consistent among different individuals than that through the oral route.

Recently, the sublingual administration of misoprostol has been studied for medical abortion. A pharmacokinetic study compared the absorption kinetics of the oral, vaginal and sublingual routes of administration of misoprostol [8]. It was found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability, as measured by the AUC, when compared to other routes. It was shown that the peak concentration was achieved 20 min after sublingual and oral administration, whereas the vaginal route of administration took an hour to reach the peak concentration. Therefore, sublingual and oral misoprostol may have the quickest onset of action. Administration of 400 µg of misoprostol by the sublingual route achieved a peak concentration of 574.8 pg/ml, as compared to 287.6 and 125.2 pg/ml attained by the oral and vaginal administration of the same dose, respectively. This finding indicates that absorption into the circulation from under the tongue is very rapid and effective. The avoidance of first-pass metabolism via the liver allows the achievement of a higher peak concentration by sublingual administration than by oral administration.

The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. Systemic bioavailability, as measured by the AUC in the first 6 h, was greatest for sublingual administration. In contrast to the previous study by Zieman et al. [7], the AUC<sub>360</sub> values after oral and vaginal administration were similar and were only 54% and 58%, respectively, of that achieved after sublingual administration. The difference in the findings on the bioavailability of these two studies may be due to the wide variation in the absorption of misoprostol through the vaginal epithelium among different women. On the other hand, although vaginal absorption was slower and although the peak concentration achieved by the vaginal route was lower than that of the other routes of administration, the serum level of misoprostol was sustained at a low level for a longer period of time. In fact, at the end of 6 h, the serum level of misoprostol acid after vaginal administration was higher than those of the sublingual and oral routes. Therefore, the effect of misoprostol may persist for >6 h after a single vaginal dose. Although the clinical effect of this low serum level is difficult to ascertain, the serum level can increase if vaginal misoprostol is repeatedly administered at an interval shorter than 6 h. Recently, a direct vagina-to-uterus transport was described for progesterone absorption [9,10]. A similar mechanism for misoprostol absorption may exist and can explain the more favorable clinical effects with vaginal administration when compared to oral administration despite similar bioavailabilities.

The misoprostol tablet was not manufactured and developed for use by routes other than the oral route. It is not uncommon to identify remnants of the tablet hours after vaginal administration, indicating that its absorption is variable and incomplete. This may be due to variation in the amount and pH value of vaginal discharge in different women, and the variation in the amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal epithelium. Numerous attempts to improve the absorption of vaginal misoprostol have been made. The addition of water to misoprostol tablets is a common practice. However, the bioavailability of vaginal misoprostol, as shown by the AUC<sub>360</sub>, was not improved by adding water to the tablets, indicating that adding water to the tablets does not improve its absorption.

### **3. Different routes and dosages of administration of misoprostol for medical abortion at <9 weeks of gestation**

The regimens using a combination of mifepristone and prostaglandin analogues have been shown to be the most effective medical method for the termination of pregnancy in the first trimester up to 9 weeks of gestation. The regimen involves the use of 200–600 mg of mifepristone given 36–48 h before the administration of a single dose of

prostaglandin analogue. The registered dose of mifepristone used for medical abortion in the first trimester is 600 mg. However, several studies have shown that 200 mg is as effective as 600 mg for this purpose [11,12]. As discussed earlier, misoprostol is the prostaglandin analogue of choice since it is inexpensive, stable at room temperature and easily available. Following the use of mifepristone, an acceptable complete abortion rate can be achieved using a single dose of misoprostol. These regimens avoid the use of repeated doses of misoprostol, which is associated with more side effects and a longer induction–abortion interval.

### 3.1. Oral misoprostol

Misoprostol is licensed for oral use. An oral dose of 400 µg of misoprostol in combination with mifepristone is effective up to seven completed weeks of pregnancy. The clinical protocol that is licensed for medical abortion in France, other European countries and the United States involves 600 mg of oral mifepristone followed 48 h later by the administration of 400 µg of oral misoprostol. However, the complete abortion rate with 400 µg of oral misoprostol, when combined with mifepristone, declines with increasing gestational age. With this regimen, the complete abortion rate was 92%, 83% and 77% for gestational ages of <49, 50–56 and 57–63 days, respectively [13]. The clinical efficacy of oral misoprostol decreases with gestational age. This is probably related to the pharmacokinetic properties of oral administration. Although the plasma level reaches the peak in a shorter period of time, the total bioavailability of oral misoprostol is lower than those with other routes of administration. The plasma level drops below the therapeutic level before it can exert an adequate clinical effect on the uterus. As a result, a single dose of oral misoprostol is not an effective regimen for medical abortion beyond 7 weeks of gestation. A regimen that involves repeated doses of oral misoprostol might maintain the plasma level at the expense of an increase in the incidence of side effects due to a higher peak concentration. Therefore, the combination of mifepristone and oral misoprostol is not an optimal regimen for medical abortion at >49 days of gestation.

### 3.2. Vaginal misoprostol

Clinical studies have demonstrated that the vaginal route of administration was more potent than the oral route for medical abortion, and the side effects were also less frequent [14]. The complete abortion rate achieved by using mifepristone followed by 800 µg of vaginal misoprostol administered 48 h later was 95–98% in up to 63 days of gestation [14–17]. The median induction–abortion interval is 4 h after the administration of misoprostol. Most of the abortions can be managed on a day-patient basis. The vaginal route of administration was more potent than the oral route in medical abortion [14]. The complete abortion rate of oral misoprostol was only 87% even when a dosage of 800 µg was used. The incidence of the gastrointestinal

side effects of oral misoprostol was also higher than that of vaginal misoprostol. The pharmacokinetic properties of oral and vaginal misoprostol can explain why vaginal misoprostol is superior. The plasma level is maintained at a low level for a longer period of time after a single dose of vaginal misoprostol, whereas a similar dose of oral misoprostol results in a rapid decline in the plasma level within the first few hours. The low but sustained level of misoprostol after vaginal administration may exert a prolonged effect on the uterus and results in regular uterine contractions. The use of mifepristone pretreatment can sensitize the uterus and thus results in an adequate clinical effect despite the low plasma level of misoprostol [18]. The peak concentration of misoprostol after a single dose of vaginal misoprostol is not high when compared to oral misoprostol. This can explain why vaginal administration is associated with fewer side effects.

### 3.3. Sublingual misoprostol

The use of the sublingual route of administration of misoprostol has been studied recently for medical abortion in the early first trimester. It has been shown in the pharmacokinetic study that the time to reach the peak level is the shortest for sublingual misoprostol. This characteristic makes sublingual misoprostol most suitable for clinical applications requiring a rapid onset of action. Besides, it may be more potent than the other routes, as shown by its highest peak concentration and greatest bioavailability [8]. Sublingual misoprostol, when combined with mifepristone, should be effective in early first-trimester medical abortion since the majority of women are expected to expel the fetus 4–6 h after the administration of misoprostol. Sublingual administration can offer an alternative route of delivery to women who do not find vaginal administration acceptable. In fact, sublingual administration has been shown to be effective for first-trimester medical abortion of a conceptus <9 weeks of gestation [17]. It was shown that 800 µg of sublingual misoprostol could achieve a similar complete abortion rate when compared to a similar dose of vaginal misoprostol administered 48 h after mifepristone for a pregnancy of <9 weeks [17]. There was no ongoing pregnancy in the sublingual arm in this study compared to three ongoing pregnancies in the vaginal arm. However, the incidences of side effects were slightly higher for sublingual misoprostol. This may be related to the high peak concentration after sublingual administration. A lower dose of misoprostol may be able to reduce the incidence of side effects. Another nonrandomized trial comparing sublingual misoprostol (600 µg) to vaginal misoprostol (800 µg) after pretreatment with mifepristone for the abortion of pregnancies <9 weeks has shown that the complete abortion rate (98.9%) of the sublingual group was not reduced even when a lower dose of misoprostol was used [19]. Further randomized studies using a larger sample size are required to compare these two routes of administration of miso-

prostaglandin and to study if the dosage of sublingual misoprostol can be reduced.

#### 4. Misoprostol-alone regimen

Mifepristone can sensitize the uterus to prostaglandins so that the number of doses and the amount of misoprostol required are reduced. In places where mifepristone is not available, the misoprostol-alone regimen is the alternative for women choosing medical abortion. Without mifepristone, repeated doses of misoprostol are usually required in order to maintain a reasonably high and acceptable complete abortion rate. There has been no pharmacokinetic study on the various routes of administration of repeated doses of misoprostol. Misoprostol-alone regimens have been investigated for first-trimester medical abortion. Investigators have used various regimens of repeated doses of misoprostol with different dosing intervals. A regimen of 800 µg of misoprostol administered vaginally every 24 h for up to three doses achieved complete abortion rates in 88–91% of women who were <8 weeks pregnant [20,21]. This regimen takes several days to complete and is, therefore, inconvenient and expensive. According to the single-dose pharmacokinetic study, a shorter dosing interval is probably required to maintain the plasma misoprostol level, especially when the oral or the sublingual route is used. Another regimen using 800 µg of misoprostol (administered vaginally) as an initial dose followed by 400 µg of misoprostol (administered vaginally) every 3 h for three to four doses achieved complete abortion rates in 70–85% of women [22,23]. The complete abortion rate of repeated doses of misoprostol is not as effective as the combined mifepristone/misoprostol regimen. Moreover, the incidence of side effects is also higher with repeated doses of misoprostol. However, it may be an alternative for women who do not want surgical abortion when mifepristone is not available.

#### 5. Conclusion

Medical abortion using a combination of mifepristone and misoprostol is a useful alternative to surgical abortion in the early first trimester. The dosage and routes of administration of misoprostol determine the complete abortion rate and side effect profile. An oral dose of 400 µg of misoprostol following mifepristone is very effective for up to seven completed weeks of pregnancy. Vaginal administration is more effective than oral administration. A vaginal dose of 800 µg of misoprostol following mifepristone is effective for up to nine completed weeks of pregnancy. Preliminary studies have shown that the complete abortion rate with 600 or 800 µg of sublingual misoprostol is comparable to that of vaginal misoprostol. Further studies are required to determine the optimal dose of

this route of administration. The misoprostol-alone regimen is inferior to the combined mifepristone/misoprostol regimen, which is the method of choice whenever mifepristone is available.

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